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This is a request for filing PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Method of Assuring Drug and Drug product Identity

CORRESPONDENCE ADDRESS

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ENCLOSED APPLICATION PARTS (check all that apply)

☑ Specification Number of Pages 18
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[Page 1 of 2]

Respectfully submitted,

SIGNATURE _____ Date 9/18/03

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Method of Assuring Drug and Drug Product Identity

Field of the Invention

This invention relates generally to a method for assuring drug and drug product identity as a product makes its way from the manufacturer to the retailer.

Within the distribution system of drugs and drug products, there is a need to assure drug and drug product identity. Example scenarios include the need to identify and differentiate authentic and counterfeit drug products, and a need to assure the dispensing of the correct drug product to patients from pharmacies. This invention entails methods to monitor drug product identity of drug products within the drug product distribution system, and achieves this goal though one or more technologies. These technologies and approaches make for a rapid and accurate approach to assure drug and drug product identity, as well as a method to evade drug product from being counterfeited.

Our approach is to apply NIR spectroscopy with a manufacturing method that provides for a dynamic tag system. Future tags are not anticipatable, and perhaps not practically detectable since formulation component(s) themselves provide the tag. The manufacturing method makes use of regulatory mechanisms that were implemented in 1995 (immediate release products) and 1997 (modified release products), in order for the tag system to be dynamic, yet viable from a regulatory point of view.

NIR spectrometry is advantageous in terms of time and disposables. Analysis times are very short (e.g. 1 sec). It is sensitive to multi-component variables, as planned in the described approach. There is essentially no sample preparation. NIR is noninvasive and nondestructive. No reagents are required. Detection limits can be very low.

Description of the Invention

Counterfeit drug products are an increasing problem, particularly since counterfeiting technology has improved. There remains a need to detect counterfeit drugs, including counterfeit drugs that are similar to the counterfeited products. The invention will include but not limited to the use of near-infrared (NIR), Raman and LIF (laser induced fluorescence) spectroscopy (all possible methods will hence be referred to as spectral methods or NIR methods) to the final dosage form and/or packaging (1-36). Advantages of NIR spectroscopy include its non-invasiveness, potential for low detection limits, and rapidity of analysis (approximately seconds), including minimal or no sample preparation. The vast majority of components in pharmaceutical products exhibit a NIR spectrum.

Either or both the pharmaceutical packaging or dosage form can serve as taggants. For example, embossing, imprinting, printing, coating, dosage form size, and other identification methods can applied to change the physical appearance of the dosage form (e.g. subtle changes in logo, use of an ultraviolet-dependent dye). Such approach can be used alone or in combination with other modifications of packaging and/or changes in the dosage form (37, 38).

In particular, the components in the dosage form can be varied, approximately batch-to-batch or with some other frequency, to provide a spectral signature for the product. Components of an oral solid dosage forms (e.g. tablets or capsules) include the drug, drug impurities, drug degradents, fillers, disintegrants, binders, lubricants, glidants, colorants, flavoring agents, and coating materials. Some or all of the component levels can be modified, approximately batch-to-batch or with some other frequency, to yield a NIR spectra for the batch or set of batches. The NIR spectra would not be identical for all product batches. A certain batch of product, or certain set of product batches, will have a unique composition, and hence a unique NIR spectra. Only the manufacturer (or agents of the manufacturer) will know the composition and NIR spectra of products from a particular batch. A suspect product can be subjected to NIR analysis and cross-referenced against the authentic NIR spectra. The association between authentic product's batch number and its NIR spectra, along with the easy of measuring NIR spectra, provides a basis to combat counterfeit drugs. Of added benefit, the association between NIR spectra and batch number(s) need not be provided to regulatory agencies or enforcement officials or health care providers, who could still perform field sampling and relay NIR spectra to the manufacturer. Furthermore, past compositions (i.e. past NIR spectra) of previous batches would not be indicative of future compositions (i.e. future NIR spectra). Hence, a counterfeit effort would have no target product to counterfeit, without detection.

This approach employs the NIR region of the electromagnetic spectrum. The NIR region typically includes wavelengths between 700 nm (near the red in the visible spectrum) and 3000 nm (near the infrared stretches of organic compounds). NIR absorbance peaks originate from overtones and combinations of the fundamental (mid-IR) bands and from electronic transitions in the atoms. C-H, N-H, and O-H bonds are responsible for most of the major absorbances. NIR spectrometry is used chiefly to identify or quantify molecules, including unique hydrogen atoms. NIR spectrometry is used to analyze for water, alcohols, amines, and any compounds containing C-H, N-H, and/or O-H groups. Many other
bond combinations also provide NIR absorbance peaks

While a pharmaceutical product typically has only one formula, and while manufacturers typically avoid manufacturing changes, this new approach to combat counterfeiting relies on the availability of several (i.e. more than one) formulas for the marketed product. Fortunately, the Food and Drug Administration (FDA) allows for a range of component and composition changes in the manufacturing of products, without onerous regulatory requirements. In the case of immediate release and modified release oral solid dosage forms, changes are denoted Level 1, Level 2, and Level 3 type changes (1,2). Tables 1-9 describe these manufacturing changes. Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance; regulatory filing documentation of a Level 1 change is limited to the Annual Report. Level 2 changes are those that could have a significant impact of formulation quality and performance. Level 3 changes are those that are likely to have a significant impact of formulation quality and performance. Tests and filing documentation for a Level 2 change and a Level 3 change each vary depending upon three factors: drug therapeutic range, drug solubility, and drug permeability. Level 1 changes require less burdensome regulatory filing documentation, and represent an advantageous approach than Levels 2 or 3 to vary formulation. Hence, Level 1 changes are a preferable approach to tag authentic product, in order to evade

counterfeiting and facilitate the detection of counterfeiting through NIR spectroscopy. This approach avoids the use of a taggant that is fixed, or is one which is included in the formulation for the sole purpose as a taggant. Our approach to use the formulation's components themselves facilitates the tagging effort, and does so in a more subtle fashion, such that this tagging effort is less detectable and hence counterfeitable.

For example, for each immediate and modified release oral solid dosage forms, a filler can be modified by as much as 5% to provide a NIR spectra that tags the authentic product, and still qualifies as a Level 1 change. Given the ability of NIR spectroscopy to resolve 1% and smaller differences in formulation, a unique tag can be fabricated by varying the filler's level. Moreover, the number of unique NIR signatures can be generated in a multiplicative fashion by modulating two or more components (e.g. vary filler, disintegrant, and binder). Varying filler over 11 levels, disintegrant over 7 levels, and binder over 3 level can results in 231 unique NIR spectra, or more.

While NIR spectroscopy has some previous limited application in pharmaceutical analysis, it does not appear to be applied to combat counterfeit drugs. Our approach employs the formulation itself to provide a dynamic tag system and NIR spectroscopy. Our approach does not employ a fixed tag or a tag whose sole function is to serve as a tag, and thus subject to counterfeiting.

Our approach to apply NIR spectroscopy with a manufacturing method that provides for a dynamic tag system is novel. Future tags are not anticipatable, and perhaps not practically detectable since formulation component(s) themselves provide the tag. The manufacturing method makes use of regulatory mechanisms that were implement in 1995 (immediate release products) and 1997 (modified release products), in order for the tag system to be dynamic, yet viable from a regulatory point of view.

NR spectrometry is advantageous in terms of time and disposables. Analysis times are very short (e.g. 1 sec). It is sensitive to multi-component variables, as planned in the described approach. There is essentially no sample preparation. NIR is noninvasive and nondestructive. No reagents are required. Detection limits can be very low.

The following example is presented in order to more fully illustrate the preferred embodiments of the invention. It should in no way be construed, however, as limiting the broad scope of the invention.

Example 1

Materials. The following drug substances and excipients were used as received: aspirin (Sprectrum, Gardena; CA), prednisone (Sigma; St Louis, MO), indomethacin (Spectrum; Gardina, CA), acyclovir (Spectrum; Gardena, CA), microcrystalline cellulose (Emocel 90M, Mendell; Patterson, NY), magnesium stearate (Spectrum, Gardina, CA), croscarmellose sodium (FMC Biopolymer; Princeton, NJ), starch (Lycatab C, Roquette; Lestrem, France), and lactose monohydrate (Super-tab, The Lactose Company; Hawera, New Zealand),

Formulation Methods. Three tablet formulations were designed and evaluated for each of four drugs, such that 12 formulations were made. The four drugs were aspirin, prednisolone, indomethacin, and acyclovir, and are denoted as drug A, B, C, and D, respectively. The drugs differ in their therapeutic uses, physicochemical properties, spectral properties, and dose ranges. For each drug, three tablet formulations were fabricated. Tables 1-4 describe the composition of the 12 formulations and refer to formulations A1, A2, A3, B1, etc. In each table, the first formulations is denoted the reference formulation (i.e. A1, B1, C1, and D1 are reference formulations). For each drug, the formulations were varied within the SUPAC IR level 1 tolerances by varying one or more excipients, relative to the reference formulation, resulting in the second and third formulations (i.e. formulations A2 and A3 were variants for formulation A1; formulations B2 and B3 were variants for formulation B1).

Variant formulations were attained through the following changes, relative to the reference. For aspirin, microcrystalline cellulose was increased and decreased. For prednisone, magnesium stearate was increased and decreased. For indomethacin, microcrystalline cellulose and croscarmellose sodium were simultaneously varied. For acyclovir, microcrystalline cellulose and lactose monohydrate were simultaneously varied. In some cases the tablet weight changed.

Near-IR Methods. The formulations were scanned and analyzed by Foss NIRSystems Rapid Content Analyzer™. The following test conditions were used. Samples were placed into sealed glass scintillation vials and scanned in reflectance mode; each sample was scanned 62 times and averaged into one spectrum; the wavelength range was 400 nm to 2500 nm with samples collected every 2 nm. The raw spectral data were converted into absorbance and 2nd derivative values using Foss's Vision software package.

Also, because this device can detect the drug type and its dose this could also be used to greatly minimize the possibility of the pharmacist dispensing the wrong drug and the wrong dose of a drug

A unique NIR signature could be engineered into the packaging, much like a certificate of authenticity on a CD or commercial software package. A company could have several hundred types and assign each one with a lot number.

It should also be noted that varying the formulation to evade and detect counterfeiting is one approach in the application of spectral methods. Another approach does not make use of the intentional periodic variation of the formulation as described above.

Various applications for this technology include, but should not be limited to

1) methods to evade and detect counterfeit drug products (and counterfeit drug substances and counterfeit excipients)

2) methods to assure drug product distribution integrity (and drug substance integrity and excipient integrity)

   a. levels for monitoring drug product distribution:

      a1. pharmaceutical manufacturers

      a2. pharmaceutical wholesalers

      a3. pharmaceutical distributers

a4. pharmacies (NOTE: While others may be primarily interested in detecting counterfeit drug products, pharmacies would also be interesting in assuring the correct product is being dispensed.)

a5. pharmaceutical repackagers

a6. FDA field monitoring, as well as regulators in other countries

Typical example applications include but are not limited to

a. Evade and detect counterfeit drug products by FDA field inspectors and/or health care worker (e.g. pharmacist, nurse) working with manufacturer of the authentic product; FDA field inspectors and/or health care workers obtain NIR spectrum of suspect products and relay the spectrum data to the manufacturer of the authentic product. Agents of the manufacturer of the authentic product may also inspect samples in the field by obtaining NIR spectrum of suspect products.

b. A pharmacy employs NIR to assure that the dispensing robot dispenses the correct product.

c. A pharmacy employs NIR to assure the dispensed product is the correct product (e.g. NIR built into tablet/capsule counter, a semi-automated dispensing device). (e.g. to avoid accidental overdose or misadventure in pharmacy dispensing)

Brief Description of the Figures

Table 1. Level 1 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Table 2. Level 2 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Table 3. Level 3 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Table 4. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Table 5. Level 2 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Table 6. Level 3 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Table 7. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Table 8. Level 2 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Table 9. Level 3 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Table 10. Schematic of possible areas of use for this invention within the commercial pipeline

Table 11. Composition of Aspirin Formulations

Table 12. Composition of Prednisone Formulations

Table 13. Composition of Indomethacin Formulations

Table 14. Compositions of Acyclovir Formulations

Table 15. 2nd Derivative of Absorbance vs. Wavelength: Aspirin Formulations

Table 16. 2nd Derivative of Absorbance vs. Wavelength: Prednisone Formulations

Table 17. 2nd Derivative of Absorbance vs. Wavelength: Indomethacin Formulations

Table 18. 2nd Derivative of Absorbance vs. Wavelength: Acyclovir Formulations

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Table 1. Level 1 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 5%
Disintegrant starch other	 +/- 3% +/- 1%
Binder	+/- 0.5%
Lubricant calcium or magnesium stearate other	 +/- 0.25% +/- 1%
Glidant talc other	 +/- 1% +/- 0.1%
Film coat	+/- 1%

Table 2. Level 2 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 10%
Disintegrant starch other	 +/- 6% +/- 2%
Binder	+/- 1%
Lubricant calcium or magnesium stearate other	 +/- 0.5% +/- 2%
Glidant talc other	 +/- 2% +/- 0.2%
Film coat	+/- 2%

Table 3. Level 3 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	Greater than +/- 10%
Disintegrant starch other	 Greater than +/- 6% Greater than +/- 2%
Binder	Greater than +/- 1%
Lubricant calcium or magnesium stearate other	 Greater than +/- 0.5% Greater than +/- 2%
Glidant talc other	 Greater than +/- 2% Greater than +/- 0.2%
Film coat	Greater than +/- 2%

Table 4. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 5%
Disintegrant starch other	 +/- 3% +/- 1%
Binder	+/- 0.5%
Lubricant calcium or magnesium stearate other	 +/- 0.25% +/- 1%
Glidant talc other	 +/- 1% +/- 0.1%
Film coat	+/- 1%

Table 5. Level 2 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 10%
Disintegrant starch other	 +/- 6% +/- 2%
Binder	+/- 1%
Lubricant calcium or magnesium stearate other	 +/- 0.5% +/- 2%
Glidant talc other	 +/- 2% +/- 0.2%
Film coat	+/- 2%

Table 6. Level 3 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	Greater than +/- 10%
Disintegrant starch other	 Greater than +/- 6% Greater than +/- 2%
Binder	Greater than +/- 1%
Lubricant calcium or magnesium stearate other	 Greater than +/- 0.5% Greater than +/- 2%
Glidant talc other	 Greater than +/- 2% Greater than +/- 0.2%
Film coat	Greater than +/- 2%

Table 7. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Release Controlling Excipient Content in the Modified Release Solid Oral Dosage Form
Any release controlling excipient(s)	+/- 5%

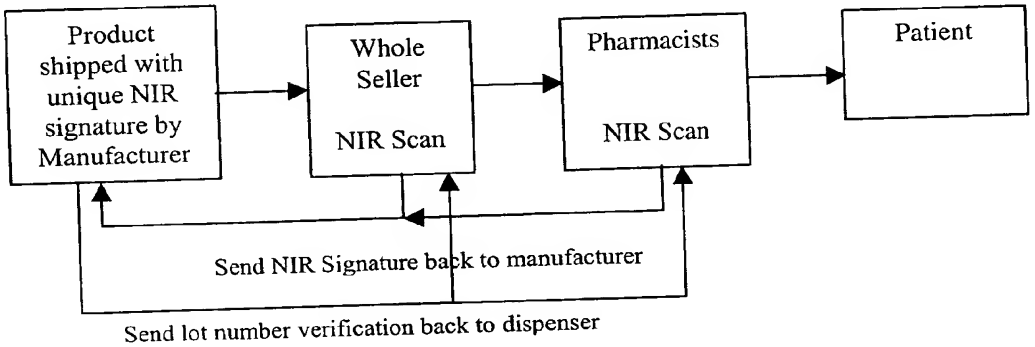
Table 8. Level 2 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Release Controlling Excipient Content in the Modified Release Solid Oral Dosage Form
Any release controlling excipient(s)	+/- 10%

Table 9. Level 3 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Release Controlling Excipient Content in the Modified Release Solid Oral Dosage Form
Any release controlling excipient(s)	Greater than +/- 10%

Basic strategy: Unique signature could be on drug produce or packaging.



Each lot of a drug will have a unique lot number and NIR signature, either based upon the products own natural variation or the methods described above. Thus, it will be very difficult for a counterfeiter to produce the spectral signature and lot number if they are changing with each lot. Also, recall most drug produce have finite shelf life.

Table 1. Composition of Aspirin Formulations

Component	Formulation A1 (mg/tab)	Formulation A2 (mg/tab)	Formulation A3 (mg/tab)
Aspirin	325	325	325
Microcrystalline cellulose	73	83	63
Magnesium stearate	2	2	2
TOTAL WEIGHT	400	410	390

Table 2. Composition of Prednisone Formulations

Component	Formulation B1 (mg/tab)	Formulation B2 (mg/tab)	Formulation B3 (mg/tab)
Prednisone	5	5	5
Microcrystalline cellulose	94.5	94.5	94.5
Magnesium stearate	0.5	0.75	0.25
TOTAL WEIGHT	100	100.25	99.75

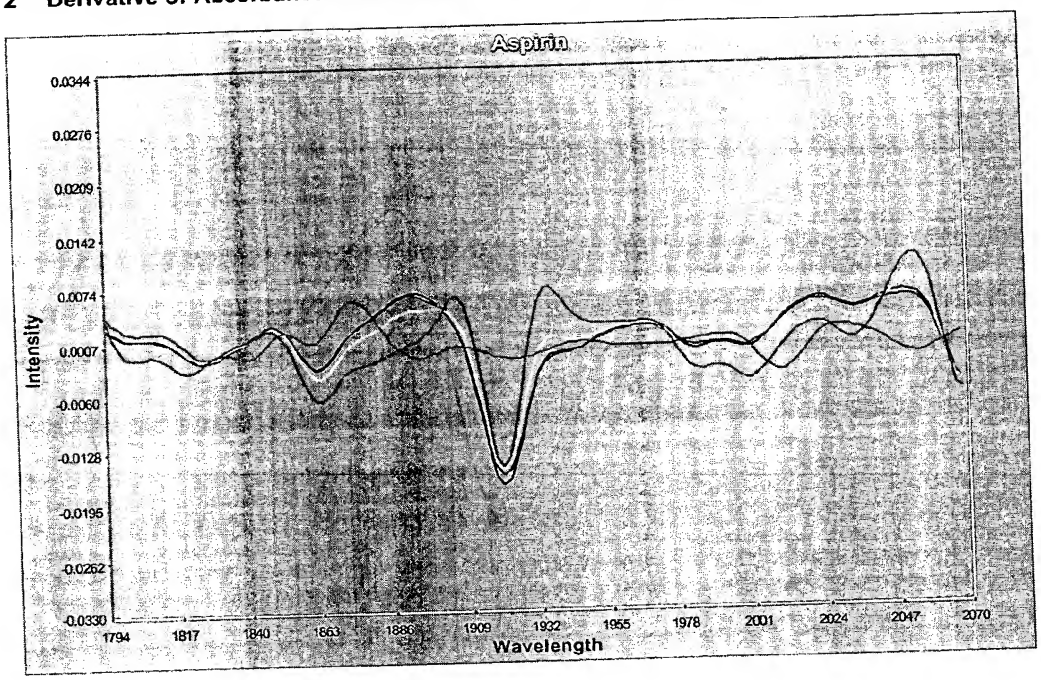
Table 3. Composition of Indomethacin Formulations

Component	Formulation C1 (mg/tab)	Formulation C2 (mg/tab)	Formulation C3 (mg/tab)
Indomethacin	25	25	25
Microcrystalline cellulose	71.5	74	69
Croscarmellose sodium	3	2	4
Magnesium stearate	0.5	0.5	0.5
TOTAL WEIGHT	100	101.5	98.5

Table 4. Composition of Acyclovir Formulations

Component	Formulation D1 (mg/tab)	Formulation D2 (mg/tab)	Formulation D3 (mg/tab)
Acyclovir	200	200	200
Microcrystalline cellulose	113.26	120.26	106.26
Starch	35	27.99	41.99
Magnesium stearate	1.75	1.75	1.75
TOTAL WEIGHT	350	350	350

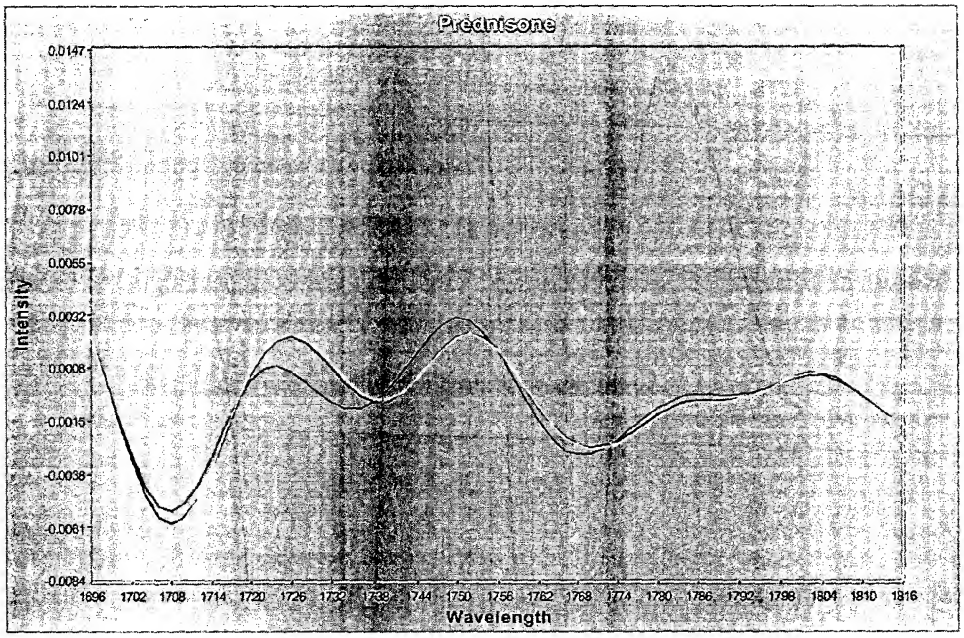
2nd Derivative of Absorbance Versus Wavelength: Aspirin Formulations



2nd Derivative of Absorbance Versus Wavelength: Aspirin Formulations. Formulations A3 (Yellow), A1 (Blue), and A2 (Red) contained increasing amounts of microcrystalline cellulose. The intensities around 1995 nm and 2055 nm reflect NIR to differentiate the formulations. The profiles of pure microcrystalline cellulose (Light Blue) and pure aspirin (Green) are also shown.

Table 15

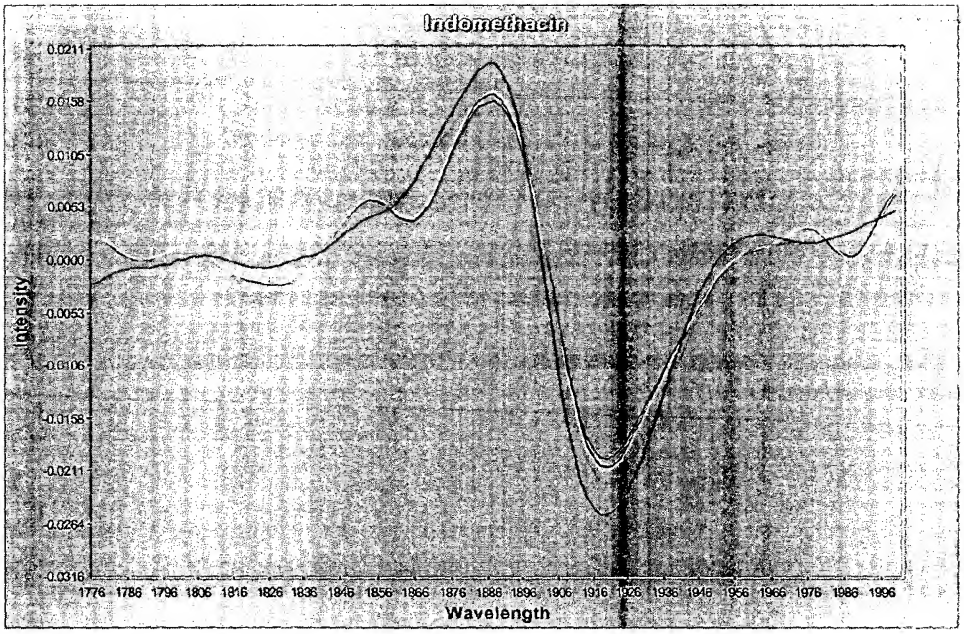
2nd Derivative of Absorbance Versus Wavelength: Prednisone Formulations.



2nd Derivative of Absorbance Versus Wavelength: Prednisone Formulations. Formulations B3 (Yellow), B1 (Blue), and B2 (Red) contained increasing amounts of magnesium stearate. The intensities around 1705 nm,as well as the regions between 1725-1735 nm and 1775-1790 nm, reflect NIR to differentiate the formulations. The profile of pure magnesium stearate (Light Blue) is also shown.

Table 16

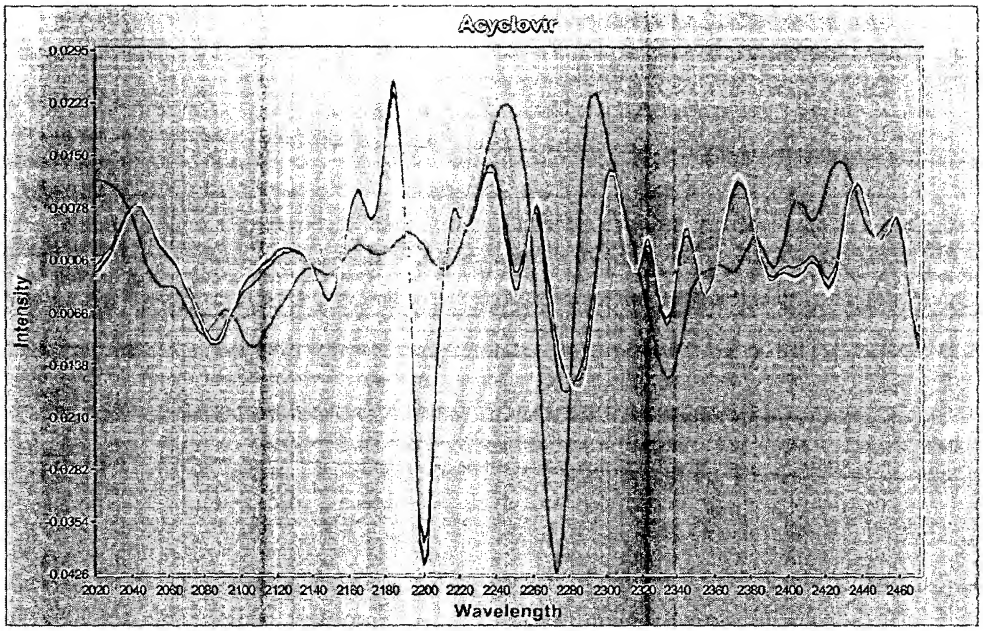
2nd Derivative of Absorbance Versus Wavelength: Indomethacin Formulations



2nd Derivative of Absorbance Versus Wavelength: Indomethacin Formulations. Formulations C3 (Yellow), C1 (Blue), and C2 (Red) contained increasing amounts of microcrystalline cellulose, as well as decreasing amounts of croscarmellose sodium. The intensities around 1890 nm and 1920 nm reflect NIR to differentiate the formulations. The profiles of pure microcrystalline cellulose (Light Blue) and pure croscarmellose sodium (Purple) are also shown.

Table 17

2nd Derivative f Absorbance V rsus Wav length: Acyclovir Formulations



2nd Derivative of Absorbance Versus Wavelength: Acyclovir Formulations. Formulations C3 (Yellow), C1 (Blue), and C2 (Red) contained increasing amounts of microcrystalline cellulose, as well as decreasing amounts of starch. The intensities around 2175 nm, 2205 nm, 2225 nm, 2250 nm, 2265 nm, 2320 nm, 2345 nm, 2365 nm, as well as the regions between 2100-2130 nm and 2380-2420 nm, reflect NIR to differentiate the formulations. The profiles of pure microcrystalline cellulose (Gray) and pure starch (Light Blue) are also shown.

Table 18